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January 27, 2005

BY FEDERAL EXPRESS

Mr. Douglas I. Ellsworth
District Director
New Jersey District Office
Food and Drug Administration
10 Waterview Blvd., 3d Floor
Parsippany, New Jersey 07054

Attn: Mercedes Mota, Compliance Officer

Re: **Pharmachem Laboratories, Inc.;**
PHASE 2 STARCH NEUTRALIZER®
Your File No.: 05-NWJ-02
FLH File No. 870008-5006

Dear Mr. Ellsworth:

On behalf of our client Pharmachem Laboratories, Inc. of Kearny, New Jersey, we make this submission in response to the warning letter dated November 19, 2004 issued by your office.

As noted in our interim letter of November 29, 2004, Pharmachem believes that competent and reliable evidence does exist that adequately substantiates the claims mentioned in your letter.

This submission contains:

(i) a legal analysis of the governing regulatory standards; and

(ii) an analysis of the results of a substantial number of clinical investigations demonstrating the effectiveness of Pharmachem's dietary supplement PHASE 2 STARCH NEUTRALIZER®, an extract of white kidney bean (*Phaseolus vulgaris*), in:

(a) aiding weight loss when consumed in a finished dietary supplement product accompanied by a healthy diet;

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(b) reducing the absorption of dietary starch, the attribute of PHASE 2® by which weight loss is effected; and

(c) neutralizing the digestive enzyme alpha-amylase, the mechanism of action by which PHASE 2® reduces starch absorption.[1]

The analysis of the substantiating data herein is made in accordance with the format prescribed by the FDA's "Guidance for Industry: Substantiation for Dietary Supplement Claims Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act" (November 2004).

I. LEGAL ANALYSIS

A. PHASE 2® is a Dietary Supplement under DSHEA

Pharmachem believes that the following is the appropriate regulatory analysis for PHASE 2®.

21 U.S.C. § 321(ff), the statutory definition of the term "dietary supplement" enacted by the Dietary Supplement Health and Education Act of 1994 ("DSHEA"), defines a dietary supplement in pertinent part as:

> "(1) a product intended to supplement the diet that bears or contains one or more of the following dietary ingredients: ...
>
> (E) a dietary substance for use by man to supplement the diet ... or
>
> (F) a[n] extract of any ingredient described in clause...(E)."

PHASE 2® falls squarely within this statutory definition of a dietary supplement, in that it bears or contains a dietary ingredient, namely, a highly concentrated, purified, standardized water-extract of a dietary substance (white kidney bean), for human use to supplement the diet. As such, PHASE 2®, from an FDA regulatory standpoint, is governed by the provisions of DSHEA.[2]

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[1] Pharmachem also sells the subject product under the registered trademark PHASE 2®, which the ingredient will be called hereafter for ease of reference.

[2] While the dietary supplement definition notes that a supplement is a food as opposed to a drug, this is simply Congress' directive in DSHEA that, contrary to FDA's previous regulatory approach in certain cases, a dietary supplement should not be regulated as a

B. Structure/Function Claims for PHASE 2® under DSHEA

One of DSHEA's provisions permits a dietary supplement to make so-called "structure/function" claims in labeling. Such claims can "describe the role of a ... dietary ingredient intended to affect the structure or function in humans," and can "characterize the documented mechanism by which a ... dietary ingredient acts to maintain such structure or function." 21 U.S.C. § 343(r)(6)(A).

The claims cited in your letter of November 19, 2004 are clearly structure/function claims authorized by 21 U.S.C. § 343(r)(6)(A), in that they describe the role of PHASE 2® in affecting body structure -- promoting weight loss -- by affecting the digestive function in reducing the absorption of starch. Certain of the claims also characterize the documented mechanism by which the reduction of starch absorption occurs, namely, by neutralizing the digestive enzyme alpha-amylase.

Each of these structure/function claims may be made for PHASE 2®, provided Pharmachem "has substantiation that the statement is truthful and not misleading." 21 U.S.C. § 343(r)(6)(B). Pharmachem respectfully submits that the clinical data presented in this response constitute the requisite substantiation.[3]

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drug. However, this statement does not support a regulatory analysis, such as that in your November 19, 2004 letter, which does not mention DSHEA and treats a dietary ingredient as any food ingredient. Notably, in other warning letters to certain end-use marketers of PHASE 2® in finished dietary supplement products, FDA has acknowledged that the same or similar claims cited in the letter to Pharmachem are structure/function claims governed by DSHEA. (See, e.g., FDA letters to Nature's Sunshine Products and Vitaminlab, both dated October 22, 2004).

[3] Notwithstanding the "structure/function" character of these claims, there is a viable question as to whether FDA has enforcement jurisdiction over the claims noted in you letter of November 19, 2004. These claims, as the letter acknowledges, have been made on Pharmachem's website, but the website does not include an offer to sell PHASE 2®, so there is no integrated transaction or distribution scheme in which the claims and the product are presented together. See *United States v. An Article of Drug ... Sterling Vinegar and Honey*, 333 F.2d 157 2d Cir. 1964). As such, the claims are advertising claims rather than labeling claims, and FDA's enforcement jurisdiction under DSHEA only extends to labeling claims. In any event, the studies presented in this submission establish that the claims at issue are substantiated, which is the matter raised by your letter.

FDA should note certain additional points:

- Pharmachem is primarily a developer and manufacturer of dietary ingredients. Generally, the company does not manufacture finished dietary supplement products.

- PHASE 2® is supplied by Pharmachem in bulk to the trade only (manufacturers and marketers of finished dietary supplements). The product is not sold directly to consumers.

- PHASE 2® is a unique product in the dietary supplement industry: it is sold by a dietary ingredient supplier yet is backed by extensive current research that supports claims for finished dietary supplements in which it is contained.

- Pharmachem has acted responsibly, not only in assuring that its structure/function claims are supported by valid data, but in assuring that its customers adhere to supportable claims. Pharmachem has instituted a license agreement with its customers, whereby finished dietary supplement manufacturers and marketers who want to use PHASE 2 ® in their products must sign a license agreement to purchase the product and use the PHASE 2® trademark. This license agreement requires such customers to use claims for their finished supplement products containing PHASE 2® that are adequately substantiated.

II. ANALYSIS OF CLAIM SUBSTANTIATION

FDA's Structure/Function Claim Substantiation Guidance adopts the following substantiation standard: that a structure/function claim for a dietary supplement be supported by "competent and reliable scientific evidence." (Guidance, p. 2). Such evidence can consist of "tests, analyses, research, studies or other evidence based on the experience of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results." *Id.*

The Guidance further recommends that the following factors be assessed in determining whether this standard is met for a given claim: (a) the meaning of the claim; (b) the relationship of the evidence to the claim; (c) the quality of the evidence; and (d) the totality of the evidence. *Id.* The studies included by Pharmachem in this submission supporting the claims cited in your letter of November 19, 2004 are analyzed below in the context of these four factors.

A. The Claims: Their Meaning

The following claims are cited in the November 19, 2004 letter:

- "Phase 2® ... 'neutralizes' the digestive enzyme alpha amylase before it can convert starch into glucose and then fat. Essentially it allows the carbohydrates to pass through the system possibly with less caloric intake."
- " ... new, standardized extract, Phase 2™, has been successfully clinically studied to 'neutralize' dietary starch absorption by over 70%, with slow, steady stimulant-free weight loss."
- "Several clinical studies of Phase 2 Starch Neutralizer™ have demonstrated efficacy in weight loss."
- " ... has been clinically & scientifically proven to neutralize starch...."
- "Phase 2® is a safe yet powerful nutritional ingredient, clinically studied to reduce the absorption of starch calories." [4]

These claims reasonably convey the following primary messages to the intended audiences (manufacturers of finished dietary supplement products and consumers):

- That PHASE 2® has been shown in human studies to produce weight loss.
- That PHASE 2®, a dietary ingredient, has been shown in human studies to reduce the absorption of starch from consumed foods, which is the attribute of the product responsible for the product's weight loss effect.
- That PHASE 2® reduces starch absorption by neutralizing the digestive enzyme alpha-amylase, which is the mechanism of action by which the product reduces starch absorption.

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[4] Pharmachem has discontinued the additionally-cited claims "Phase 2® allows you to enjoy those foods that you love without all the calories," and PHASE 2® "improves post-prandial glucose tolerance."

B. Relationship of the Evidence to the Claims

There are a number of scientific studies demonstrating that PHASE 2® promotes weight loss, reduces starch absorption, and neutralizes alpha-amylase. Before describing how these studies relate to the claims at issue, it will be useful to review background information on the relationship of alpha-amylase to starch absorption, the reduction of starch absorption, and the relationship of this phenomenon to weight loss.

(1) Background

Alpha-amylase is secreted in saliva and by the pancreas, and is responsible for breaking down starch for absorption. A substance able to bind to alpha-amylase can prevent the digestion and subsequent absorption of starch (in the form of complex carbohydrates consumed through the diet). The result can be a decrease in the effective caloric content of that food, promoting a loss of weight over time.

(2) Starch Digestion and Absorption

Dietary carbohydrate is available in several forms, primarily in naturally-occurring plant-based starches, which are found in vegetables, fruits, cereals and legumes. These starches consist of complex carbohydrates and are the starches of interest here.

Digestion of starch begins with alpha-amylase in the mouth, and continues in the duodenum using alpha-amylase and other enzymes from the pancreas. The end result of digestion of starch is the production of disaccharides that are absorbed by the small intestine. The final conversion from disaccharides to monosaccharides (glucose) occurs during absorption. Once absorbed, glucose is delivered to the liver and enters into intermediary metabolism. Glucose in excess of the immediate energy requirements of the body is stored either as glycogen in the liver and in skeletal muscle, or is converted to fatty acids and triglycerides and stored in adipose tissue, contributing to body weight. Starch hydrolysis by alpha-amylase is the rate limiting step in starch digestion.[5]

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[5] Hiele M, Ghoos Y, Rutgeerts P, Vantrappen G. Starch digestion in normal subjects and patients with pancreatic disease, using a 13CO2 breath test. *Gastroenterology* 1989; 96(2 Pt 1):503-509.

(3) Mechanism of Action

Neutralizing alpha amylase can prevent the digestion of starches. The end result of inhibiting this enzyme may be a decrease in the number of calories absorbed from the food containing the starch.

The white kidney bean (*Phaseolus vulgaris*) has documented salivary and pancreatic alpha-amylase inhibitory effects. *Phaseolus vulgaris* binds to alpha- amylase in non-competitive fashion, optimally at a pH of 5.5. Similar binding can be seen at neutral pH as well.

(4) Studies: Relationship to the Claims

Criteria prescribed by FDA's Structure/Function Claim Substantiation Guidance relevant to the "relationship of the evidence to the claim" factor are: (a) whether the studies measured the dietary supplement that is the subject of the claim; (b) whether the studies measured the body structure or function that is the subject of the claim; whether the studies were based on a population similar to the population that will be consuming the dietary supplement; and (d) whether the claim accurately conveys to consumers the nature, extent and level of scientific certainty of the effect achieved in the studies (Guidance, p. 4).

Pharmachem presents in this submission studies which have measured the effect of PHASE 2® or, in the case of mechanism of action studies, the effect of a similar white bean extract, on the body structure or function communicated by the above-noted claims, in normal populations. The effects achieved in these studies are accurately conveyed to consumers by the claims at issue, in terms of the nature and extent of the claims and the level of scientific certainty afforded by the studies, as evidenced by the analysis herein.

C. <u>The Quality of the Evidence</u>

The studies submitted herewith comprise competent and reliable scientific evidence of the claims made. Each of the trials is summarized below, and the reports of the studies are annexed.

(1) Weight Loss Studies

Studies measuring the effect of PHASE 2® in producing weight loss:

Tab A:

- **Tiberi L, Celleno L. Evaluation of a Dietary Supplement for Safety and Effectiveness in Reducing the Intake of Calories from Complex Carbohydrates as Compared to a Placebo (Double-blind use test). EVIC ITALIA Rome, Italy 2001; Scripps Clinic Conference, Natural Supplements in Evidence-Based Practice: 1-18-04.**

Study Design and Conduct: This study utilizing a Phase 2® product (Blockal batch D106B in the study) for weight reduction was conducted in Italy in 2001. 60 overweight subjects participated in a randomized, double-blind, placebo- controlled clinical trial consisting of a 30 day run-in phase followed by a 30 day active phase. Subjects were between ages 20 and 45, were 5-15 kg overweight, and their weight had been stable during the preceding 6 months. During a run-in phase subjects were educated on the test diet with included a 2000-2200 calorie diet with a complex carbohydrate intake concentrated in one of the two main meals of the day. In addition, subjects were asked not to change the current activity/exercise. Subjects received either a combination product containing 444.8 mg of Phase 2® or placebo before the main carbohydrate containing meal of the day. (The Blockal™ product also contained chromium picolinate, but at the clinically insignificant level of 50 mcg, well below the amount of 400 mcg reported in other trials to produce weight loss).

Results: The Phase 2® group lost an average of 2.933kg (6.45 lbs) in 30 days compared with an average of 0.348 kg (0.766 lbs) in the placebo group, a clinically and statistically significant difference ($p<0.001$). Body composition was measured with bioelectrical impedance, and the Phase 2® group demonstrated a 10.45% reduction in body fat compared with a 0.16% reduction in the placebo group, also a difference of clinical and statistical significance ($p<0.001$). Waist and hip circumferences were measured as well, and the Phase 2® group demonstrated 2.93 cm and 1.48 cm reductions respectively compared with 0.46cm and 0.11cm reductions in the placebo group ($p<0.001$), again, a difference of clinical and statistical significance.

Tab B:

- **Rothacker D. Reduction in Body Weight with a Starch Blocking Diet Aid: Starch Away Comparison with Placebo. Report, Leiner Health Products, 8-2003.**

Study Design and Conduct: A 12-week study of Phase 2® in a soft-chew formulation was completed in 2003. In this randomized, double-blind, placebo controlled trial of 60 overweight individuals subjects were given 1000mg of Phase 2® before each meal (six 500mg soft-chews per day). Subjects received education on proper eating habits and the importance of exercise, but were not given a specific diet or exercise regimen.

Results: The results of this study demonstrated statistically significant weight reduction in the Phase 2® group compared with placebo at weeks 6 (p=0.013) ,8 (p=0.031), and 12 (=0.029). The amount of weight lost by the active group at 12 weeks was 6.9 pounds (average of 0.575 pounds per week), while the placebo group gained 0.8 lbs.

Tab C:

- **Udani J, Hardy M, Madsen D. Blocking Carbohydrate Absorption and Weight Loss: A Clinical Trial using Phase 2 Brand Proprietary Fractionated White Bean Extract. *Alternative Medicine Review* 2004; 9:63-69.**

Study Design and Conduct: A randomized, double-blind, placebo-controlled study of 39 obese subjects (BMI 30-43) were randomly allocated to receive either 1500mg of Phase 2® or identical placebo. 27 subjects completed the study (14 active and 13 placebo). They were instructed to take the test product with lunch and dinner each day for 8 weeks. The product was taken with at least 8 oz of water. Subjects began a controlled high fiber/low fat diet at the beginning of the study that provided 100 to 200 g of complex carbohydrate intake per day. Carbohydrate intake was recommended for the subjects on the basis of estimated daily maintenance carbohydrate requirement. Subjects were instructed to eat the majority of their carbohydrates during lunch and dinner since those were the meals at which the Phase 2® or placebo were taken.

Results: The study results at 8 weeks demonstrated that the Phase 2® group lost an average of 3.79 lbs. (an average of 0.47 lbs. per week), compared with the placebo group which lost an average of 1.65 lbs. (an average of 0.21 lbs. per week).

This was a positive trend in favor of the Phase 2® group, although the difference was not statistically significant (two tailed p-value = 0.35). Similar trends were seen at 2, 4 and 6 weeks. Triglyceride levels in the Phase 2® group were almost significantly reduced by an average of 26.3 mg/dL, compared with the 8.2mg/dL drop seen in the placebo group (p=0.07).

Tab D:

- **Singh BB. Phase 2 (*Phaseolus vulgaris*) for Short-Term Weight Loss. Report, 1-27-2004.**

Study Design and Conduct: In 2003, 27 overweight (BMI 25-30) subjects participated in a 30-day randomized, double-blind, placebo-controlled trial of 1000 mg of Phase 2® or identical placebo twice a day. Subjects were also given nutritional guidelines and breakfast and lunch foods were provided to increase compliance. In addition, subjects met with a personal trainer to establish an exercise program, and had a counseling session with a behavioral psychologist to identify psychological barriers to weight loss.

Results: 25 subjects completed the study. At 4 weeks, the active group had lost 6.0 lbs and the placebo group had lost 4.7 lbs. While both groups had lost significant weight compared with their baseline (p=0.0002 active and p=0.0016 placebo), between group analysis was not significant (p=0.4235). When subjects were stratified by Dietary Carbohydrate Intake, the tertile that took in the most carbohydrates demonstrated significantly greater loss of body weight compared with the placebo group (8.7 pounds vs. 1.7 pounds, p=0.0412). The same tertile demonstrated a significantly greater loss in inches around the waist (3.3 inches for the Phase2 group and 1.3 inches for the placebo group, p=0.0100).

Tab E:

- **Erner S, Meiss DE. The Effect of Thera-Slim™ on Weight , Body Composition and Select Laboratory Parameters in Adults with Overweight and Mild-Moderate Obesity. Report, 2004.**

Study Design and Conduct: A 24-week randomized, double-blind, placebo-controlled crossover to open label study was performed in 2003. Sixty (60) overweight and obese subjects were randomized to receive either 1500 mg of TheraSlim™ (1000 mg of Phase 2® and 500 mg of fennel seed (*Foeniculum vulgare)* powder or placebo with lunch and dinner. After 12 weeks all subjects were put on TheraSlim™ in an open-label fashion and followed for another 12 weeks.

Subjects were asked to eat a diet in which lunch and dinner contained 100-200g of carbohydrates. The primary outcomes were change from baseline in weight, BMI, blood pressure, cholesterol, insulin and glucose.

Results: During the randomized, controlled portion of the trial, there were some significant data points for weight loss compared to placebo when the data were stratified for dietary compliance (fair to good compliance).

(2) Reduction of Starch Absorption Studies

Studies measuring the effect of PHASE 2® in reducing the absorption of starch from a carbohydrate-containing meal, the clinical effect which is responsible for weight loss:

Tab F:

- **Vinson JA. In Vivo Effectiveness of a Starch Absorption Blocker in a Double-Blind Placebo Controlled Study with Normal Subjects. University of Scranton. Report, 9-9-2003.**

Study Design and Conduct: A three-arm crossover study was performed on 20 subjects comparing 515 mg Phase 2®, 750mg of Phase 2® (in powder form mixed in with the food), and placebo (47). The standardized meal was 64g of carbohydrates (including 6 g dietary fiber and 19 g sugars). Serial glucose levels were measured every 10 minutes for 60 minutes using the One Touch Ultra blood glucose monitoring system.[6]

Results: The 750 mg Phase 2® demonstrated significantly lower blood glucose levels at 10, 20 and 30 minutes ($p<0.01$) compared with the 515 mg dose and compared with placebo. The 515 mg Phase 2® group showed significantly lower

[6] Measurement of plasma glucose levels is a validated method for measuring starch absorption. Kennedy, F P, Miles J M, Heiling V, Gerich, J E. The effect of two new alpha-glucosidase inhibitors on metabolic responses to a mixed meal in normal volunteers. *Clin Exp Pharmacol Physiol* 1987; 14:633-640; Wang Z, Wang G, He M., Yang Y. Digestive and absorptive characteristic of starches determined in vitro and in vivo. *Wei Sheng Yan Jiu* 2004; 33:470-472 (Chinese); Willms B, Lubke D, Ahrens K, Arends J. Delayed absorption of carbohydrates in the therapy of Type II diabetes: comparison between dietary (Muesli) and pharmacological (Alpha-glucosidase inhibition) modification. *Schweiz Med Wochenschr* 1991; 121:1379-1382(German).

blood glucose at 10, 20 ($p<0.01$), and at 30 minutes ($p<0.05$) compared with placebo. The area under the curve was lower in the 750 mg Phase2™ group compared with both the 515mg dose group and the placebo group, but did not reach statistical significance ($p<0.1$).

Tab G:

- **Vinson JA. Dose-Response Pilot Study of Phase 2 Efficacy as an Inhibitor of Glucose Absorption with a Full Meal. University of Scranton. Report, 3-22-04.**

Study Design and Conduct: Seven subjects participated in a crossover study comparing 750mg of Phase 2® with placebo after a standardized meal containing 64g of carbohydrates (including 6g dietary fiber and 19g sugars) (46). Serial plasma glucose levels were taken for 2 hours after consumption of the meal and Phase 2®.

Results: Glucose levels were lower on average for subjects at all time points in the Phase 2® group, except at 20 minutes where the values were equivalent. The overall area under the curve was 28% lower in the Phase 2® group compared with placebo, and 42% when the contribution of simple sugars was removed, although statistical significance was not reached at particular time points or for the area under the curve comparison.

Tab H:

- **Vinson J. Investigation of the efficacy of Phaseolamin 2250 (Phase 2), a purified bean extract from Pharmachem Laboratories. University of Scranton. Reports, 9-2001.**

Study Design and Conduct: Ten (10) healthy subjects participated in a randomized, double-blind, crossover single meal study comparing Phase 2® with placebo. After an overnight fast, all subjects were given a standardized meal containing 60 g of carbohydrates (white bread) with either 1500 mg of Phase 2® or placebo. Plasma glucose was then measured every 30 minutes for 4 hours. After 1 week, the subjects crossed over and repeated the procedure with the other test product.

Results. The Phase 2® group demonstrated lower average glucose levels at all time points and an average 57% reduction in the area under the curve compared with the placebo group. Statistical analysis between groups was not provided.

Tab I:

- **Vinson J. In Vivo Effectiveness of a Starch Absorption Blocker in a Double-Blind Placebo-Controlled Study with Normal College-Age Subjects. University of Scranton, Report, November, 2001.**

Study Design and Conduct: This single meal study was conducted in normal subjects who were required to remain sedentary during the active portion of the study. The dose of the Phase 2® was 1500 mg and the carbohydrate content of the meal was 60 g from white bread. Serial blood draws for occurred after 2 hours. Four of ten subjects were evaluated; two dropped out and four others were excluded as non-absorbers in that the area under the glucose-time curve was negative.

Study Results: The area under the curve in the Phase 2® group was calculated to be 85% lower than the placebo curve ($p<0.05$), although the Phase 2® group did not demonstrate statistically significant differences at individual time points.

The above body of Vinson data corroborate earlier studies showing a significant reduction in starch absorption by a partially-purified white bean extract similar to PHASE 2®, when compared to placebo. See, e.g.:

Boivin M, Zinsmeister AR, Vay, LW Go, DiMagno, EP. Effect of a Purified Amylase Inhibitor on Carbohydrate Metabolism of After a Mixed Meal in Healthy Humans. *Mayo Clin Proc* 1987; 62(4):249-255 **(Tab J);**

Jain NK, Boivin M, Zinsmeister AR, Brown ML, Malagelada JR, DiMagno EP. Effect of Ileal Perfusion of Carbohydrates and Amylase Inhibitor on Gastrointestinal Hormones and Emptying. *Gastroenterology* 1989; 96(2 Pt 1):377-387 **(Tab K).**

(3) Alpha-Amylase Neutralization Studies

Studies measuring the effect of white bean extracts in neutralization of the digestive enzyme alpha-amylase, the mechanism of action by which Phase 2® reduces starch absorption: [7]

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[7] The mechanism of action studies presented in this submission evaluated white kidney bean extracts very similar PHASE 2®. Data on the same type of dietary supplement (here, a white bean extract, just like PHASE 2®), by appropriate test methodology, is adequate proof of advertising claim substantiation under FTC standards (*In re Metagenics*, 1996 FTC LEXIS 459,*54-55(1996); *In re Pfizer*, 1972 FTC LEXIS 13,*101), and FDA has adopted

Tab L:

- **Layer P, Carlson GL, DiMagno EP. Partially purified white bean amylase inhibitor reduces starch digestion in vitro and inactivates intraduodenal amylase in humans. *Gastroenterology* 1985; 88(6): 1895-1902.**

Study Design and Conduct: This Mayo Clinic (Rochester, MN) study of 7 subjects who underwent gastro-duodenal intubation demonstrated that increasing concentrations of a partially purified white bean extract caused increasing amounts of amylase inhibition in a dose dependent manner. Patients had continuous infusions of amino acids to stimulate pancreatic secretions and also had continuous aspiration of gastric and duodenal contents.

Results: Amylase activity was measured from these aspirations and this study demonstrated 94%, 99% and 99.5% inhibition of amylase at 2.0, 3.5, and 5.0 mg/ml infusions of the amylase inhibitor.

Tab M:

- **Layer P, Zinsmeister AR, DiMagno EP. Effects of decreasing intraluminal amylase activity on starch digestion and postprandial gastrointestinal function in humans. *Gastroenterology* 1986; 91(1):41-48.**

Study Design and Conduct: Four volunteers at the Mayo Clinic were intubated with an oroileal tube. Subjects were given 50g of rice starch with either placebo, 5g of white bean extract, or 10g of white bean extract. Part of the placebo and white bean extract dose were given at the beginning of the meal to inactivate the alpha amylase present in the intestinal lumen before the meal. The remainder of the dosage was delivered during the middle of the meal.

Results: The white bean extract significantly reduced duodenal, jejunal, and ileal intraluminal amylase activity by more than 95% in as soon as 15 minutes and for as long as 2 hours. It also increased the delivery of carbohydrates to the small bowel by

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the FTC's "competent and reliable scientific evidence" standard for structure/function labeling claim substantiation (FDA Structure/Function Claim Guidance, at 2). Note that all other studies in this submission evaluated the effect of PHASE 2® itself.

22-24% and increased breath H2 concentrations.[8] Additionally, it showed significant lowering of glucose, insulin, c-peptide, and gastric inhibitory polypeptide level.

Tab N:

- **Gibbs B, Alli I: Characterization of a purified alpha-amylase inhibitor from white kidney bean (Phaseolus vulgaris). *Food Research International* 1998; 31:217-225.**

Study Design and Conduct: An extract from white kidney bean (*Phaseolus vulgaris*) was prepared. Fractions were separated by HPLC and measured for alpha-amylase inhibition by the method of Frels and Rupnow (1984). Under this method, alpha-amylase solution is added to each fraction sample, and one unit of alpha-amylase inhibitory activity is defined as the amount of inhibitor which causes 10% inhibition of the enzyme in 5 minutes.

Results: The fraction with the highest inhibitory activity was fraction 12, which produced 5258 total inhibitory activity units, and 8765 such units when further purified. This fraction was characterized as a glycoprotein whose deglycosylated molecular weight was 54,857 when measured by electrospray ionization mass spectrometry. Its binding constant was 2.8 μM at 55°C.

D. Totality of the Evidence

In this submission, Pharmachem has presented five randomized, double-blind, placebo controlled clinical studies demonstrating the effect of PHASE 2® in promoting weight loss. Two of these studies (Tiberi, Celleno and Rothacker) were conducted independently and without the prior knowledge of Pharmachem, and produced clinically and statistically significant ($p<0.05$) differences in favor of PHASE 2® in reducing weight by an average of 6.45 and 6.90 pounds, respectively, over 4 weeks and 12 weeks, respectively. The Udani, Erner and Singh studies support these findings by showing that PHASE 2® produced pronounced trends in

[8] The hydrogen breath test is also a validated method for measuring starch absorption. B Flourie, C Florent, F Etanchaud, D Evard, C Franchisseur and JC Rambaud. Starch absorption by healthy man evaluated by lactulose hydrogen breath test. INSERM U290, Hopital Saint-Lazare, Paris, France.

weight loss favoring PHASE 2® (Udani), a significant difference ($p<0.05$) in weight loss favoring PHASE 2® (8.7 lbs. vs. 1.7 lbs.) when subjects were stratified by dietary carbohydrate intake (Singh), and a significant difference in weight loss when subjects were stratified by body mass index and compliance (Erner).

The four Vinson studies, taken together (34 evaluated subjects, crossover design) demonstrate that PHASE 2® reduced starch absorption when compared to placebo by producing lower average plasma glucose levels (an accepted measurement of starch absorption) at all time points measured, or a lower average reduction in area under the curve. These data corroborate earlier studies by Boivin and Jain on similar partially purified white bean extracts.

The 1985 and 1986 Mayo Clinic studies showed that a partially purified white bean extract very similar to PHASE 2® reduced starch digestion by inhibiting the alpha-amylase enzyme in a dose dependent manner. The Gibbs study also showed that a purified fraction of white kidney bean extract, again very similar to PHASE 2®, produced substantial alpha-amylase inhibition activity *in vitro*.

Taken as a whole, this body of data substantiates Pharmachem's claims that PHASE 2® promotes weight loss by reducing starch absorption by the mechanism of inhibiting the activity of the alpha-amylase digestive enzyme.

III. CONCLUSION

Pharmachem maintains that the data in this submission substantiates the claims made for PHASE 2® raised in your letter of November 19, 2004.

Pharmachem is continuing to study the effects of this important product. In this respect, Pharmachem is playing a unique and pioneering role for a dietary ingredient supplier in the supplement industry.

The significance of a dietary ingredient that has been scientifically proven to promote weight loss by reducing starch absorption is readily apparent from the New Dietary Guidelines recently issued by FDA's parent department, the U.S. Department of Health and Human Services, urging American consumers, faced with a potential epidemic of obesity, to reduce weight by controlling caloric intake (see **Tab O**).

Pharmachem representatives and I stand ready to meet with appropriate FDA officials to discuss this submission, if necessary, to discuss the substantiating data

submitted herein, and to resolve any remaining questions arising from by your November 19, 2004 letter.

If there are no further issues, Pharmachem requests written confirmation from FDA that the data in this package satisfy FDA's substantiation standard for PHASE 2® for the claims involved.

Sincerely yours,

Charles J. Raubicheck

CJR/bav

cc(w/encl.): Joseph R. Baca
Susan Walker, Ph.D.
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